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Meeting Abstract

Role of NKT cells to assist priming of antigen-specific T-cell responses

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T-cell responses to natural infection are orders of magnitude greater than those observed in cancer patients in response to current vaccination protocols. It is most likely, therefore, that optimizing tumor vaccination protocols will require a deeper understanding of the signals that the immune system coordinates in order to respond to pathogenic infection. Compounds that mimic these signals may therefore be exploited as adjuvants in current tumor vaccination strategies.

Background

We are now gaining a clearer understanding of the cellular events leading to effective T-cell mediated immunity. Dendritic Cells (DC) lay at the heart of this process, acquiring, processing and presenting antigens to T cells, and effectively serving as 'nature's adjuvants' by providing the co-stimulatory machinery and cytokine environment necessary to hone appropriate T-cell response. DC reside in peripheral tissues in an immature state defined by significant capacity to acquire antigens, but low capacity to stimulate T cells. Upon exposure to pathogenic insult, DC undergo a maturation process involving migration to lymphoid sites, down-regulation of the rate of antigen uptake, and increased expression of MHC molecules on the cell surface bearing processed fragments from the acquired antigens. These changes enable the DC to promote the activation and proliferation of those naive T cells with T-cell receptors that specifically recognize antigenic peptides in the context of MHC molecules.

The potency of DC as antigen presenting cells for naive T cells can be modulated directly by signals received from pathogenic organisms themselves through pattern recognition receptors on the DC, of which Toll-like receptors (TLR) are the prime examples. The form that these signals take will define the size of T-cell response the DC initiates, and functional quality of the T cells induced in terms of types of factors released (cytokines) and cytolytic capacity.

Tumors, on the other hand, are unlikely to be able to provide these crucial signals to DC. Cancer vaccines should therefore be designed with this knowledge in mind, with emphasis given to compounds that stimulate DC via pattern recognition receptors to induce appropriate Type 1-biased cellular immunity.

Results

We are currently examining the possibility of exploiting these different DC stimuli in the design of vaccines. Enhanced CD8+ and CD4+ T-cell immunity is observed following administration of soluble protein antigen with alpha-galactosylceramide (alpha-GalCer), a ligand for invariant CD1d-dependent Natural Killer-like T cells (*i*NKT cells). Activation of *i*NKT cells with alpha-GalCer, or an analogue with a truncated sphingosine chain, OCH, induces modification of dendritic cell function *in vivo*, providing mature cells with enhanced immunostimulatory capacity. This adjuvant activity enhances both the priming and boosting of cytotoxic T lymphocyte (CTL) responses to a number of peptide and protein antigens, including a clinically relevant, HLA-A2-restricted epitope derived from the human tumor antigen NY-ESO-1. These data highlight the potential for the use of *i*NKT cell-ligands in heterologous prime-boost strategies. CTL responses induced in the presence of *i*NKT cell stimulation eradicated established tumors, while responses induced without this adjuvant activity were ineffective. Interestingly, oral administration of antigen together with alpha-GalCer was capable of providing potent CTL with restimulatory capacity, despite the fact that this route of administration, in the absence of alpha-GalCer, induces blunted responses.

Together these data demonstrate that activation of iNKT cells can enhance weak immunization procedures, highlighting the therapeutic potential for iNKT cell activation as an effective vaccine adjuvant.